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(54) Title: MACROPHAGE SCAVENGER RECEPTOR ANTAGONISTS

(57) Abstract

Macrophage scavenger receptor antagonists are provided. Methods of treating cardiovacular disease comprising administration of the present compounds are also provided. The present compounds inhibit lipid accumulation within macrophage–derived foam cells.

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MACROPHAGE SCAVENGER RECEPTOR ANTAGONISTS

FIELD OF INVENTION

Cardiovascular diseases are the leading cause of death in the U.S., accounting annually for more than one million deaths. Atherosclerosis is the major contributor to coronary heart disease and a primary cause of non-accidental death in Western societies. Since the prevention of atherosclerosis is an enormous unmet medical need, considerable effort has been made in defining the etiology and potential treatment of atherosclerosis and its consequences, including myocardial infarction, angina, organ failure and stroke. Despite this effort, there are many unanswered questions including how and when atherosclerotic lesions become life-threatening, the best point of intervention, and how to detect and monitor the progression of lesions.

There is widespread agreement that multiple risk factors contribute to atherosclerosis including hypertension, elevated total serum cholesterol, high levels of low density lipoprotein ("LDL") cholesterol, low levels of high density lipoprotein ("HDL") cholesterol, diabetes mellitus, severe obesity, and cigarette smoking. To date, treatment of atherosclerosis has been narrowly focused on treating elevated cholesterol levels and modifying lipids has become the major focus of treatment and research.

However, recent studies have indicated that 40% of deaths due to coronary disease occurred in men with total cholesterol levels of below 220 mg/dl. It is thus obvious that too great an emphasis is being placed on lipid lowering. Indeed, only 30% of patients with atherosclerosis have elevated lipid levels, indicating that other pathogenic factors are involved. A logical scenario for future therapies and preventive measures should therefore include a multidisciplinary approach consisting of diet modification, HMG-CoA reductase inhibition and novel therapies aimed directly at plaque growth and stability.

The initial lesion in atherosclerosis is the fatty streak, which arises from cholesteryl esters maintained as lipid droplets inside macrophage-derived foam cells. Macrophages down-regulate their LDL receptors and instead express mRNA and undergo new protein synthesis for a novel receptor for modified LDL. This receptor recognizes all modified forms of low-density lipoprotein and has come to be known as the macrophage scavenger receptor ("MSR"). If the macrophage is present in an environment that is continually generating modified LDL, it will accumulate lipid droplets of cholosteryl esters, continuing

until the macrophage dies from its toxic lipid burden. The released lipid then forms the acellular necrotic core of the atherosclerotic lesion. Subsequent recruitment of fibroblasts, vascular smooth muscle cells and circulating monocytes and T-lymphocytes complete the inflammatory response and formation of the mature atherosclerotic plaque. Macrophage-derived foam cells are concentrated in the shoulders of plaques, where their secreted proteases and collagenases may contribute to plaque rupture which may lead to a fatal thrombotic event.

Plaque regression, a function of the dynamic balance among initiation, progression, stabilization and removal of plaque constituents, has been unequivocally demonstrated in humans as well as in numerous animal models. Multiple regression studies in non-human primates have shown that even relatively advanced lesions regress over time when atherogenic dietary stimuli are discontinued or pharmacological regimens are initiated.

Inhibition of lipid accumulation within macrophage-derived foam cells by utilizing MSR antagonists is expected to prevent plaque initiation, retard plaque progression, and initiate plaque regression through the process of "reversed cholesterol transport" to acceptor HDL. Thus, MSR antagonists provide a unique approach towards the pharmacotherapy of cardiovascular diseases such as atherosclerosis, coronary artery disease, renal disease, thrombosis, transient ischemia due to clotting, stroke, myocardial infarction, organ transplant, organ failure, and hypercholesterolemia.

SUMMARY OF THE INVENTION

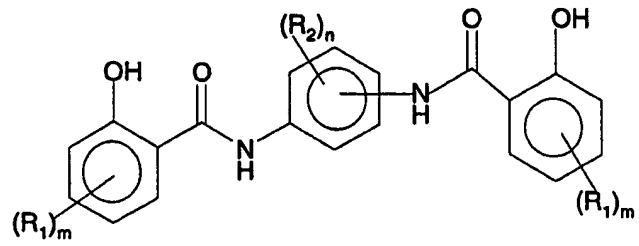
The present invention involves phenylenediamine compounds represented by Formula (I) hereinbelow and their use as macrophage scavenger receptor ("MSR") antagonists which are useful in the treatment of a variety of cardiovascular diseases including but not limited to atherosclerosis, coronary artery disease, renal disease, thrombosis, transient ischemia due to clotting, stroke, myocardial infarction, organ transplant, organ failure and hypercholesterolemia.

The present invention further provides methods for antagonizing the macrophage scavenger receptor in animals, including humans, comprising administering to an animal in need of treatment an effective amount of a compound of Formula (I), indicated hereinbelow.

The present invention further provides methods of inhibiting lipid accumulation within macrophage-derived foam cells.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are selected from Formula (I) hereinbelow:



Formula (I)

wherein :

R^1 is independently selected from the group consisting of hydrogen, alkyl, $(R_1)_2$ N-alkyl, hydroxyalkyl, carboxy, carboxyalklyl, fluoroalkyl, halo, haloaryl, aryl, heteroaryl, hydroxy, amino, alkylamino, and alkoxy; or R^1 represents a fused ring forming a naphthalene moiety with the six membered aryl ring it substitutes;

m is an integer from 1 to 4.

R^2 is independently selected from the group consisting of hydrogen, R^1-benzamido, R^1-benzyl ether, R^1-benzylamino, amino, halo, hydroxy, alkoxy, alkyl, fluoroalkyl, cyano, nitro, aryloxy, nitroalkyl, aryl, and 1,2-benzo; or the R^2 moiety represents a fused ring forming a napthalene ring with the six membered aryl ring it substitutes; and

n is an integer from 1 to 3.

Preferably, R^1 is selected from the group consisting of hydrogen, 5-trifluoromethyl, 5-chloro, 5-bromo, 3-bromo, 4-bromo, 5-bromo-3-phenyl, 5-iodo, 5-iodo-3-phenyl, 2-phenyl, 3-phenyl, 5-phenyl and 3-methoxy. More preferably, R^1 is 5-trifluoromethyl or 5-bromo.

Preferably, any R^2 aryl substituents are selected from the group consisting of hydroxy, halo, aryl, alkyl, cyano, nitro, R^1- benzamidyl; alkoxy and aryloxy. More preferably, R^2 is selected from the group consisting of 2-chloro, 3,4-dichloro, 4,5-dichloro, 3-methoxy, 2-isopropyl, 3-cyano, 4-butyl, 2-nitro, 2-phenoxy, 2-nitro-4-methyl, 2-phenyl, 4-phenyl, 2-benzamidyl, 1,2-benzo. Most preferably, R^2 is 4,5-dichloro, 2-benzamidyl, 4-bromo, 4-phenyl or 4-butyl.

Particularly preferred compounds useful in the present invention include: bis-N,N'-(5-bromo-2-hydroxybenzoyl)-4,5-dichloro-1,2-phenylenediamine, bis-N,N'-(5-bromo-2-hydroxybenzoyl)-1,2-phenylenediamine, bis- N,N'-(5-trifluoromethyl-2-

hydroxybenzoyl)-1,2-phenylenediamine, bis-N,N'-(5-trifluoromethyl-2-hydroxybenzoyl)-4,5-dichloro-1,2-phenylenediamine, bis-N,N'-(3-phenyl-2-hydroxybenzoyl)-4,5-dichloro-1,2-phenylenediamine, and bis-N,N'-(3-phenyl-2-hydroxybenzoyl)-1,2-phenylenediamine.

The present compounds can also be formulated as pharmaceutically acceptable salts and complexes thereof. Pharmaceutically acceptable salts are non-toxic salts in the amounts and concentrations at which they are administered.

Pharmaceutically acceptable salts for use when basic groups are present include acid addition salts such as those containing sulfate, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

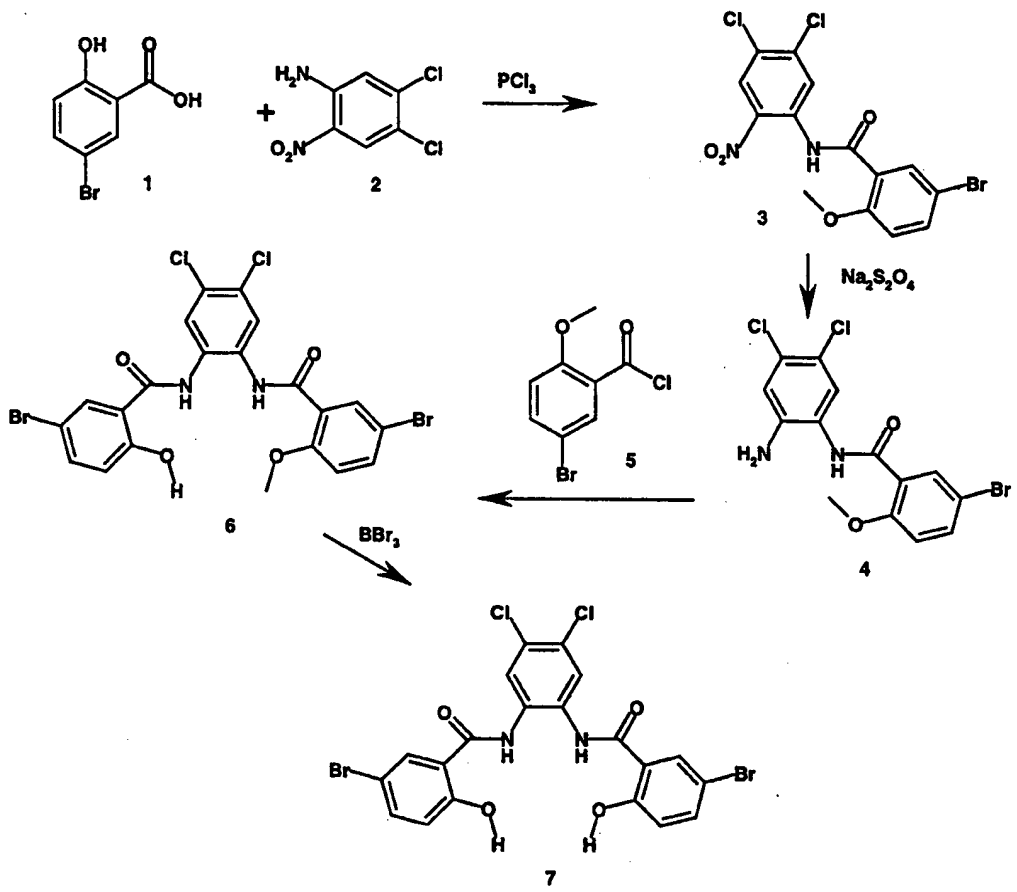
Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present.

The present invention provides compounds of Formula (I) above which can be prepared using standard techniques. An overall strategy for preparing preferred compounds described herein can be carried out as described in this section. The examples which follow illustrate the synthesis of specific compounds. Similar 1,2-phenylene diamide compounds have been reported by Y. A. Ibrahim and A. H. M. Elwahy; *Synthesis,* 503 (1993); F. C. Anson et al., *J. Am. Chem. Soc.*, Vol. 108, 6593 (1986). Similar 1,3-phenylenediamine diamide compounds have been reported by VanAllan, *J. Am. Chem. Soc.* Vol 69, 2913 (1947) and Fargher et al., *J. Textile Inst.* Vol 21, 245 (1930); also 1,4-phenylene diamides in US 2,754,209 (1952). Using the protocols described herein as a model, one of ordinary skill in the art can readily produce other compounds of the present invention.

In the following synthetic examples, temperature is in degrees Celsius (°C). Unless otherwise indicated, all of the starting materials were obtained from commercial sources. Without further elaboration, it is believed that one skilled in the art can, using the description provided in this specification, utilize the present invention to its fullest extent. These Examples are given to illustrate the invention, not to limit its scope. Reference is

made to the claims for what is reserved to the inventors hereunder.

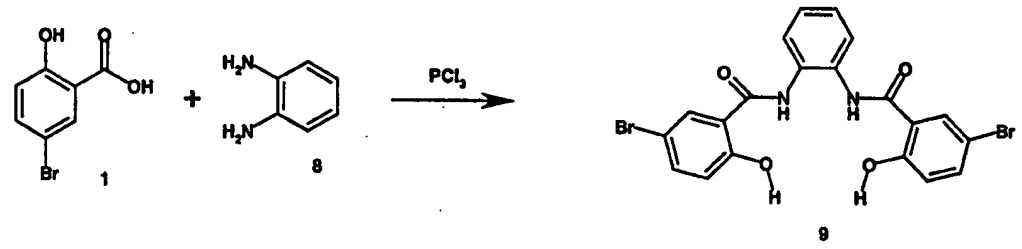
Scheme 1



Heating a salicylic acid with a 2-nitroaniline in the presence of phosphorous trichloride gives a 2'-nitrosalicylanilide. A convenient procedure is to reflux the reactants in chlorobenzene as described by Lemaire, Schramm, and Cahn, *Journal of Pharmaceutical Sciences,* Vol. 50, pp 831-837, incorporated herein in its entirety by reference. This product can be converted to a 2'-aminosalicylanilide by reduction. One convenient reagent for this purpose is sodium hydrosulfite which effects the reduction without removing any aromatic halogen atoms. The amine can be reacted with a 2-methoxybenzoyl chloride to give the bis-amide, and the methoxy ether cleaved to the phenol by a variety of known cleavage reagents. Boron tribromide is especially effective. This procedure can be used to conveniently obtain unsymmetrical bis-amides by using different salicylic acids for the first and seacond stages of the sequence. This procedure can also be used to prepare 1,3- and

1,4-bis-amides by starting with 3- or 4-nitroanilines in place of the 2-nitroanilines described above.

Scheme 2



An alternative method of obtaining symmetrical bis-amides is outlined in Scheme 2. A mixture of two moles of a salicylic acid and one mole of a 1,2-phenylenediamine is heated with a condensing agent such as phosphorous trichloride to give the product in one step.

Example 1

Bis-N,N'-(5-Bromo-2-hydroxybenzoyl)-4,5-dichloro-1,2-phenylenediamine

a. 5-Bromo-3',4'-dichloro-6-nitrosalicylanilide (3)

A mixture of 2.17 g (10 mmol) of 5-bromosalicylic acid, 2.07 g (10 mmol) of 3,4-dichloro-6-nitroaniline, and 0.44 ml (0.637 g, 5 mmol) of phosphorous trichloride in 30 ml of chlorobenzene was refluxed under argon for 3.5 hr. The hot reaction mixture was filtered and on standing at 25° for 18 hr. gave 1.82 g of yellow-orange crystals. Recrystallization from methylene chloride-hexane gave 1.22 g of bright yellow crystals, mp 197-198.5°C.

b. 2'-Amino-5-bromo-4'5'-dichlorosalicylanilide (4)

A mixture of 3 (1.22 g, 3 mmol), 5% aqueous $NaHCO_3$ (100 ml) and THF (100 ml) was treated with 27 g of $Na_2S_2O_4$ in 1.5 g portions over a several hour period. Filtration of the reaction mixture followed by concentration of the THF layer under vacuum gave a solid which was dissolved in 75 ml of hot methanol, filtered, and concentrated to 10 ml and chilled to -78°C to give straw yellow crystals, mp 293-295°C.

c. N-(5-Bromo-2-hydroxybenzoyl)-N'-(5-bromo-2-methoxybenzoyl)-4,5-dichloro-1,2-phenylenediamine (6)

A mixture of 4 (376 mg, 1.0 mmol), Na_2CO_3 (318 mg, 3 mmol) and 10 ml of acetone was treated with a solution of 375 mg (1.5 mmol) of 3-bromo-6-methoxybenzoyl chloride in 10 ml of acetone and stirred for 18 hr. The reaction mixture was poured into 100 ml of water and filtered to give a cream colored powder which was recrystallized from toluene to give straw yellow crystals, mp 241-244°C.

d. bis-N,N'-(5-Bromo-2-hydroxybenzoyl)-4,5-dichloro-1,2-phenylenediamine

A stirred suspension of **6** (150 mg, 0.25 mmol) in 25 ml of CH_2Cl_2 under argon was treated with a 1M solution of BBr_3 (0.75 ml, 0.75 mmol). After 4 hr. the reaction mixture was diluted with 15 ml of MeOH, stirred for 15 min. and then concentrated under vacuum to give a solid residue. Recrystallization from toluene gave a light gray powder, mp 281-281.5°C.

Example 2

bis-N,N'-(5-Bromo-2-hydroxybenzoyl)-1,2-phenylenediamine

A mixture of 1,2-phenylenediamine (1.00 g, 9.24 mmol) and 5-bromosalicylic acid (3.81 g, 17.56 mmol) in 15 ml of chlorobenzene under argon was treated with PCl_3 (1.27 g, 9.24 mmol) and refluxed for 4.5 hr. Filtration of the hot reaction mixture and chilling of the filtrate gave a colorless powder which was recrystallized from an ethanol-water mixture to give colorless crystals, mp 253.5-256°.

With appropriate manipulation and protection of any chemical functionality, synthesis of the remaining compounds of Formula (I) is accomplished by methods analogous to those above and to those described in the Experimental section.

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The present compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional

oral dosage forms such as capsules, tablets, and liquid preparations such as syrups, elixirs, and concentrated drops.

Alternatively, injection (parenteral administration) may be used, *e.g.*, intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the compounds of the invention are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and re-dissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories.

For topical administration, the compounds of the invention can be formulated into ointments, salves, gels, or creams, as is generally known in the art.

The amounts of various compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC_{50}, EC_{50}, the biological half-life of the compound, the age, size and weight of the patient, and the disease or disorder associated with the patient. The importance of these and other factors to be considered are known to those of ordinary skill in the art.

Amounts administered also depend on the routes of administration and the degree of oral bioavailability. For example, for compounds with low oral bioavailability, relatively higher doses will have to be administered.

Preferably the composition is in unit dosage form. For oral application, for example, a tablet, or capsule may be administered, for nasal application, a metered aerosol dose may be administered, for transdermal application, a topical formulation or patch may be administered and for transmucosal delivery, a buccal patch may be administered. In each case, dosing is such that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.01 to 500 mg/Kg, and preferably from 0.1 to 50 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. The daily dosage for parenteral, nasal, oral inhalation, transmucosal or transdermal routes contains suitably from 0.01 mg to 100

mg/Kg, of a compound of Formula (I). A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I). The active ingredient may be administered from 1 to 6 times per day, preferably once, sufficient to exhibit the desired activity, as is readily apparent to one skilled in the art.

As used herein, "treatment" of a disease includes, but is not limited to prevention, retardation and prophylaxis of the disease.

The MSR receptors described in the present application belong to a recently classified group designated the SR-A group and exist in two forms, type A-I and type A-II, which arise through differential exon splicing of a single gene. The terms "MSR" and "SR-A" are used interchangeably in the present application.

Diseases and disorders which might be treated or prevented, based upon the affected cells, include atherosclerosis, coronary artery disease, renal disease, thrombosis, transient ischemia during clotting, stroke, organ transplant, organ failure, myocardial infarction and hypercholesterolemia.

Composition of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil. olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

No unacceptable toxological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests.

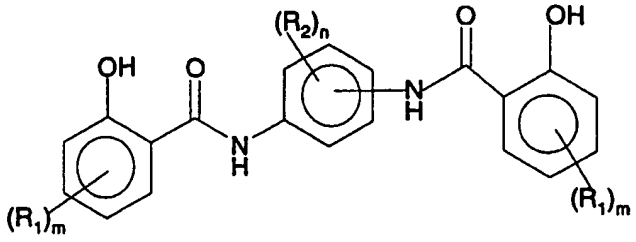
Assays of MSR activity, both degradation and binding/internalization, were adapted from Goldstein et al., "Receptor-mediated Endocytosis of Low-density Lipoprotein in cultured Cells," *Methods Enzymol.*, 98:241-260 (1983); incorporated herein in its entirety by reference. Briefly, 293 cells transfected with MSRI or II are seeded at 10^5 cells/ml/well in a 24-well dish in Eagle's Minimal Essential Medium with 2 mM glutamine, 10% FCS and 0.4 mg/ml geneticin. After 2 days, the medium is replaced with 500µl fresh serum-free medium containing 2 mg/ml BSA and 125[I]-AcLDL (iodinated acetylated low density lipoprotein) at 5µg/ml, and cells are incubated at 37C for 5 hours. After this suitable period for ligand degradation, cells are removed to a 4C cold room. Supernatant is removed into trichloroacetic acid, and the mixture is centrifuged. The supernatant is chloroform-extracted in order to isolate 125[I]-monoiodotyrosine, the degradation product of 125[I]-AcLDL, and portions are counted to determine degradative activity. To determine cell-associated ligand, cell monolayers are washed and incubated at 4C with ice-cold buffer "A" containing 150 mM NaCl, 50 mM Tris-HCl, and 2 mg/ml BSA, pH 7.4, to eliminate nonspecifically bound counts. Cells are washed three times rapidly with 1 ml, incubated twice for 10 min each on a rotary shaker in 1 ml buffer A, then washed twice rapidly in 1 ml buffer A without BSA. After aspiration of all wash buffer, cells are lysed in 0.1N NaOH and removed to counting vials for determination of binding/uptake and subsequent protein determination (Pierce BCA protein assay). The present actives yield IC_{50} values of <50 um in degradation assays and <100um in binding/uptake assays.

The fluorescent compound DiI-AcLDL (1,1'-dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate-labeled LDL) has also been shown to be a useful tool in assessing activity of the macrophage scavenger receptor (Freeman et al., *Proc. Natl. Acad. Sci., USA*, 88:4931-4935 (1991); Penman et al., *J. Biol. Chem.*, 266:23985-23993 (1991)). We also utilized an assay for MSR antagonists based on the uptake of DiI-AcLDL by the transfected HEK 293 cells. For most assays, HEK 293 cells transfected with SR-AI were used, although both SR-AI and SR-AII appeared to have equivalent activity in all studies performed. Briefly, HEK 293 cells were seeded at 2 x 10^4 cells/ well in a 96-well plate in EMEM with 2mM glutamine, 10%FBS and 0.4mg/ml geneticin. The assay was standardized and optimized, and testing was performed in serum-free EMEM containing 2mg/ml bovine serum albumin. Confluent cells were incubated with DiI-AcLDL (final concentration 2ug/ml) in the absence and presence of inhibitors (quadruplicate wells) for 4 hours at 37C. Following aspiration of solution and a Locke's buffer wash, results were quantified with a fluorescence plate reader at 530nm exc/590nm em.

All publications, including but not limited to patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference as though fully set forth.

What is claimed is:

1. A method of treating a cardiovascular disease or condition which comprises administering to a subject in need of treatment an effective amount of a compound having the structure of Formula (I):



Formula (I)

wherein :

R^1 is independently selected from the group consisting of hydrogen, alkyl, $(R_1)_2$ N-alkyl, hydroxyalkyl, carboxy, carboxyalkyl, fluoroalkyl, halo, haloaryl, aryl, heteroaryl, hydroxy, amino, alkylamino, and alkoxy; or R^1 represents a fused ring forming a naphthalene moiety with the six membered aryl ring it substitutes;

m is an integer from 1 to 4.

R^2 is independently selected from the group consisting of hydrogen, R^1-benzamido, R^1-benzyl ether, R^1-benzylamino, amino, halo, hydroxy, alkoxy, alkyl, fluoroalkyl, cyano, nitro, aryloxy, nitroalkyl, aryl, heteroaryl, and 1,2-benzo or the R^2 moiety represents a fused ring forming a napthalene ring with the six membered aryl ring it substitutes; and

n is an integer from 1 to 3.

2. A method according to claim 1 wherein:

R^1 is selected from the group consisting of hydrogen, 5-trifluoromethyl, 5-chloro, 5-bromo, 3-bromo, 4-bromo, 5-bromo-3-phenyl, 5-iodo, 5-iodo-3-phenyl, 2-phenyl, 3-phenyl, 5-phenyl and 3-methoxy; and

R^2 is selected from the group consisting of 4-chloro, 3,4-dichloro, 4,5-dichloro, 4-bromo, 4-methoxy, 4-isopropyl, 4-cyano, 4-butyl, 4-nitro, 4-phenoxy, 5-nitro-4-methyl, 3-phenyl, 4-phenyl, 4-benzamidyl, 4,5-benzo.

3. A method according to claim 2 wherein any R^2 aryl substituents are selected from the group consisting of hydroxy, halo, aryl, alkyl, cyano, nitro, R^1- benzamidyl, alkoxy and aryloxy.

4. A method according to claim 3 wherein R^2 is selected from the group consisting of 4,5-dichloro, 4,5-benzo, 4-phenyl, 4-bromo and 4-butyl.

5. A method according to claim 4 wherein R^1 is 5-trifluoromethyl or 5-bromo.

6. A method according to claim 5 wherein the compound is selected from the group consisting of:

bis-N,N'-(5-bromo-2-hydroxybenzoyl)-4,5-dichloro-1,2-phenylenediamine, bis-N,N'-(5-bromo-2-hydroxybenzoyl)-1,2-phenylenediamine, bis-N,N'-(5-trifluoromethyl-2-hydroxybenzoyl)-1,2-phenylenediamine, bis-N,N'-(5-trifluoromethyl-2-hydroxybenzoyl)-4,5-dichloro-1,2-phenylenediamine, bis-N-N'-(3-phenyl-2-hydroxybenzoyl)-4,5-dichloro-1,2-phenylenediamine, and (3-phenyl-2-hydroxybenzoyl)-1,2-phenylenediamine.

7. A method according to claim 1 wherein the disease or disorder is selected from the group consisting of atherosclerosis, coronary artery disease, renal disease, thrombosis, transient ischemia due to clotting, organ transplant, organ failure, stroke, myocardial infarction and hypercholesterolemia.

8. A method according to claim 7 wherein the disease or disorder being treated is atherosclerosis.

9. A method of antagonizing a macrophage scavenger receptor comprising administering to a subject in need of treatment an effective amount of a compound according to claim 1.

10. A method of inhibiting lipid accumulation within macrophage-derived foam cells by administering to a subject in need of treatment an effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/16347

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/165
US CL :514/616

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/616

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Database BIOSIS on STN, 1996, the abstract No. 412603, GIRY et al., "Characterization of inherited scavenger receptor overexpression and abnormal macrophage phenotype in a normolipidemic subject with planar xanthomas," Journal of Lipid Research. 1996, 37(7), pages 1422-1435.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 16 SEPTEMBER 1999	Date of mailing of the international search report 07 OCT 1999
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